REMARKS

Claims 1 to 24 and 28 to 60 are pending in the application. Claims 5, 6, 9, 15 to 24 and 38 to 58 are withdrawn from further consideration as being drawn to a non elected invention. In order to advance the prosecution, claims 5, 6, 9, 13 to 24 and 38 to 58 are canceled by the above amendments. After entrance of the above claim amendments, claims 1 to 4, 7, 8, 10 to 12, 28 to 37, 59 and 60 are pending the application. Claims 13 and 14 are rejected under 35 U.S.C. §112, second paragraph. All of the pending claims are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 2001/089457 in view of Berge et al., and Meade et al. and Gimenez et al. All of the pending claims are rejected under the judicially created doctrine of Obviousness-type double patenting. Applicants request reconsideration and withdrawal of the rejections for the reasons set forth herein.

I. The rejection Under 35 U.S.C. §112, second paragraph

Claims 13 and 14 are rejected under 35 U.S.C. §112, second paragraph. Claims 13 and 14 have been deleted by the above amendments.

In view of the above amendments, applicants submit that the reasons for rejection have been rendered moot and respectfully request that the rejection here be withdrawn.

II. The rejection Under 35 U.S.C. §103(a)

Claims 1 to 4, 7, 8, 10 to 12, 28 to 37, 59 and 60 are rejected as being unpatentable over WO 2001/089457 in view of Berge et al., and Meade et al. and Gimenez et al. The Examiner urges that WO 2001/089457 teaches the compound of instant claim 1 and pharmaceutically acceptable salts thereof for the currently claimed uses. The difference between WO 2001/089457 and the current invention is that the instant application claims a choline salt where no specific salt is taught or described in WO 2001/089457. The Examiner

combines WO 2001/089457 with Berge et al., indicating that the FDA previously approved one or more compounds where the compound was in the form of a choline salt, and Meade et al., for indicating that "Platelet-activating factor (PAF) is a phospholipid which, in experimental animals, has been shown, even in minute quantities, to cause a pronounced thrombocytopenia", and Gimenez et al., for indicating that cytidine 5'-diphosphocholine (CDP-choline), decreased platelet-activating factor (PAF) levels by more than 65%.

According to the rejection, Meade et al., indicates increasing PAF levels have been shown to cause thrombocytopenia, Gimenez et al., is cited as indicating CDP-choline decrease PAF levels in a rat model, therefore it would be expected that choline by itself would lead to decreased levels of PAF. Thus, one of skill in the art would have been motivated to prepare the choline salt of the subject compound with the expectation that the choline salt would provide enhanced effects in the treatment of thrombocytopenia.

Applicants request reconsideration and withdrawal of the rejection because: Berge et al., alone or in combination with Meade et al., and Gimenez et al., fail to render the claimed invention *prima facie* obvious, Meade et al., and Gimenez et al., are not within applicants' field of endeavor and should be removed as citable references, Meade et al., demonstrates that there is no established connection between PAF antagonist and the treatment of thrombocytopenia, nothing of record indicates that, at the time of the invention, choline itself acts as a PAF antagonist.

The effect of Berge et al., as a reference was discussed in the court's decision in *Pfizer v. Apotex, 488 F3rd. (Fed. Cir. 2007).* The Court in *Pfizer* specifically noted "[e]very case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts." In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992). The court also acknowledged "To be sure, to have a reasonable expectation of success, one must be

motivated to do more than merely to vary all parameters to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." Medichem, S.A. v. Rolabo, S.L., 437 F,3d 1157, 1165 (Fed. Cir. 2006). The Court noted that obviousness is a complicated subject requiring sophisticated analysis, and no single case lays out all the facets of the legal test.

The facts of the instant case are very different from the facts in *Pfizer*. In *Pfizer*, the maleate salt form of the compound amlodipine was selected for development and was in the prior art. During the development of amlodipine, the maleate salt turned sticky and hygroscopic during formulation and proved to be unacceptable. The inventors then researched and developed another more stable salt form the besylate salt.

The Court noted that Pfizer's prior art patent contained a description of salt forms suitable for use with the disclosed compounds. Specifically, the '909 patent was cited as disclosing that the pharmaceutically-acceptable acid addition salts of amlodipine are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, and gluconate salts, and that the preferred salt is maleate. In their analysis, the Court found that motivation to select a new salt partially arose from the nature of the problems encountered with amlodipine maleate. The Court noted that testimony of record evidenced that one skilled in the art would have been motivated to choose an anion having a different structure than that of maleate. That the maleate salt ion is acyclic and consists of a double bond between the carbon atoms, whereas the besylate salt ion is cyclic and lacks the same double bond. And the Court specifically concluded that the evidence clearly showed that as soon as tablet processing problems arose with the amlodipine maleate tablet formulation, Dr. Wells readily compiled a list of seven

alternative anions-including the besylate-each of which he expected would form an amlodipine acid addition salt. Moreover, the Court found that Dr. Wells' testimony reflects the fact that he believed that amlodipine besylate would solve the problems of amlodipine maleate.

In the instant case there is no indication in (WO 2001/089457) of any specific contemplated salt forms, let alone preferred salt forms. Additionally, there is no motivation to attempt to form any specific salt of any compound in view of WO 2001/089457 as no problems or inadequacies of the free compounds or salts thereof are indicated. Even if one skilled in the art wanted to attempt to form a salt of one of the compounds in (WO 2001/089457); the skilled worker would have no guidance as to how to narrow the field, where to start or which attributes may prove advantageous. As the Court noted in Pfizer "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." Medichem, S.A. v. Rolabo, S.L.

Thus, Berge et al., indicates that the FDA previously approved one or more compounds where the compound was in the form of a choline salt, while at the same time, the reference presents many more compounds where the choline salt was passed over in favor a different salt form. Berge et al., fails to establish a prima facie case for obviousness to specifically select the choline salt of the instantly claimed compound.

Moreover, there is no motivation in Meade et al. alone or together with Gimenez et al., that would lead the skilled worker to expect that the choline salt of the subject compound would have beneficial effects in the treatment of thrombocytopenia.

First, the instant application is directed to a compound that is an agonist of the TPO receptor. Meade et al., and Gimenez et al., are directed to compounds that are antagonist of PAF. There is no indication in the application, or of record, that the claimed compound acts or is expected to act as an antagonist of PAF. Because Meade et al., and Gimenez et al., are directed to antagonist of PAF and the instant application is directed to agonist of the TPO receptor, applicants contend that the skilled worker would not look to Meade et al., or Gimenez et al., for any guidance or expectation as to how the subject compound could or would act. Meade et al., and Gimenez et al.. are in a different filed of endeavor. Because the skilled worker would not look to Meade et al., or Gimenez et al., in attempting to assess the subject compound, Meade et al., and Gimenez et al., should be removed as citable references.

Second, although Meade et al., indicates that increased levels of PAF can cause thrombocytopenia, Meade et al., failed to conclude that inhibition of PAF could result in a treatment for thrombocytopenia. Of particular note is the passage of Meade et al., where the known PAF-receptor antagonist WEB 2086 was used in a clinical trial in adult-type ITP that yielded negative results (see page 664 last paragraph in the first column which carries over to the top of the second column).

Meade et al., discussed the differences between ITP and PAF-induced changes stating:

> While similarities can be drawn between TTP or septicemic thrombocytopenia and the pathology of PAF-induced changes in experimental animals, the most common form of clinically important thrombocytopenia, ITP, shows a very different histopathology from that after PAF infusion. In ITP there is no obvious microangiopathy and no evidence for fibrinogen breakdown in the blood vessels. The mechanism of removal of platelets involves principally not the lung but the spleen, which may in a few ITP patients show a modest enlargement.

> Even if, as discussed later, PAF were to be involved in the pathogenesis of ITP, it is not surprising that the histopathology of PAF-induced thrombocytopenia and ITP are so different, as it is likely that other factors (e.g. anti-platelet auto-antibodies) are involved in the clinical disease but not represented in the PAF-induced thrombocytopenia animal models. There is considerable scope for devising models in which PAF-perfused animals are either first treated with sub-maximal amounts of anti-platelet antibody or immunized to produce such antibody. The effects of PAF in the presence of an anti-platelet antibody may be quite different from the effect of PAF alone. (See page 661 second column)

Meade et al. underscores the uncertainty of the connection between PAF antagonist and the treatment of thrombocytopenia commenting:

> Clinical thrombocytopenia is a heterologous collection of diseases. It is likely that several different pathological mechanisms are involved, and the involvement of PAF in these mechanisms is still unclear. (See page 664 second column)

In the concluding paragraph, Meade et al., indicates the state of the art regarding PAF and thrombocytopenia:

> There is a need for a greater understanding of the biochemical pharmacology of PAF in relation to thrombocytopenia and hopefully such understanding will help decide if there is a place for a PAF antagonist in the therapy of any of the types of clinical thrombocytopenia.

Meade et al., clearly demonstrates that there is no established connection between PAF antagonist and the treatment of thrombocytopenia.

Third, according to the outstanding Office Action, Gimenz et al., is cited for the premise that CDP-choline decreased PAF levels by more than 65% in an assay, choline is used to synthesize CDP-choline; therefore choline is expected to decrease levels of PAF. Applicants contend that nothing in Gimenz et al., teaches or discloses that choline itself would be expected to decrease levels of PAF. Generally, when a compound is indicated as having activity, it is not expected that parts of the compound by themselves would retain the same activity. Applicants respectfully request that the Examiner indicate where Gimenz et al., provides support for the notion that choline it self would be expected to decrease PAF levels. Notwithstanding, applicants again note that, as indicated above, the connection between antagonist of PAF and thrombocytopenia was not established by Meade et al. or any of the cited prior art references.

In summary, applicants respectfully submit that: 1) Berge et al., alone or in combination with Meade et al., and Gimenez et al., fail to render the claimed invention *prima facie* obvious. 2) Meade et al., and Gimenez et al., are not within applicants' field of endeavor and should be removed as citable references. 3) Meade et al., demonstrates that there is no established connection between PAF antagonist and the treatment of thrombocytopenia. 4) Nothing of record indicates that, at the time of the invention, choline itself acts as a PAF antagonist.

In view of the above amendments and remarks applicants respectfully request that the rejection here be withdrawn.

III. The rejection for Obviousness-Type Double Patenting

Claims 1 to 4, 7, 8, 10 to 14, and 28 to 36 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over the progeny of WO 2001/089457 (U.S. Patent Nos. 7,335,649; 7,452,874; and 7,332,481). Applicants note that the

instant application is also rejected under 35 U.S.C. 103(a) for being unpatentably obvious over WO 2001/089457 which is the International Publication of the cited patents. Applicants contend the above arguments remove the obviousness rejection under 103, and thereby the rejections here for obviousness type double patenting are rendered moot.

Additionally, in making the argument that claims 1 to 4, 7, 8, 10 to 14, and 28 to 36 are rejected for obviousness-type double patenting as being unpatentable over U.S. Patent Nos. 7,335,649; 7,452,874; and 7,332,481, the Examiner cited In re Lemin, 141 USPQ 814 for the premise that the indiscriminate selection of "some" among "many" is *prima facie* obvious, and that one of skill in the art would have been motivated to make the claimed compounds with the expectation that additional compounds useful in treating thrombocytopenia would be obtained. Applicants request reconsideration and withdrawal of the rejections for the reasons set forth herein.

It is well-established that one person may obtain a valid patent on an improvement even though it is dominated by the basic or general patent of another.[1] In *In re* Kaplan (1986),[2] the Federal Circuit reversed the board's double patenting rejection and held that a double patenting rejection cannot be justified solely on the ground that the subject matter of a claim in a second patent or patent application is "dominated" by the claims in a first patent. In other words, double patenting does not arise automatically when the broader claim embraces the subject matter defined by the narrower claim.

Similarly, the court in In re Lemin (cited by the Examiner) reversed the rejection finding that nothing in the cited art suggested the criticality of the claimed range.

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[1] 3A-9 Chisum on Patents § 9.03
[2] *In re* Kaplan, 789 F. 2d 1574, 229 USPQ 678 (Fed. Cir. 1986).

The key question in considering a double patenting issue is "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?" The instant invention is directed to a specific salt form of one of the many compounds disclosed in the progeny of WO 2001/089457 (U.S. Patent Nos. 7,335,649; 7,452,874; and 7,332,481). The cited art fails to provide any motivation, guidance or suggestion as to which salt form may be beneficial when used with the selected compound. Therefore, current invention is not an obvious variant of what has been disclosed and claimed in the cited art.

In view of the comments here, and the comments under 35 U.S.C. 103(a) for being unpatentably obvious over WO 2001/089457, applicants respectfully request that the rejections here be withdrawn.

Applicants submit that all reasons for rejection have been addressed and that the claims, as amended herein, in view of the above amendments and remarks, are allowable. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned attorney at the number indicated below.

Respectfully submitted,

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